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Review Article

Research Domain Criteria as Psychiatric Nosology: Conceptual, Neuroethical, and Social Implications

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Abstract

Diagnostic classification systems in psychiatry have continued to rely on clinical phenomenology despite limitations inherent to that approach. In view of these limitations and recent progress in neuroscience, the National Institute of Mental Health (NIMH) has initiated the Research Domain Criteria (RDoC) project in order to develop a more neuroscientifically-based system of characterizing and classifying psychiatric disorders. The RDoC initiative aims to transform psychiatry into an integrative science of psychopathology in which mental illnesses will be defined as involving putative dysfunctions in neural nodes and networks. However, conceptual and methodological issues inherent to RDoC need to be addressed before any attempt at implementing use in clinical psychiatry. Neuroethical, legal and social issues can and will be fostered by the use of neuroscientific information to establish RDoC. This essay describes current progress in RDoC, defines key technical, neuroethico-legal and social issues generated by RDoC adoption and use, and posits key questions that must be addressed and resolved if RDoC are to be employed for psychiatric diagnoses and therapeutics. Specifically, we posit that objectification of complex mental phenomena may raise ethical auestions about autonomy, the value of subjective experience, what constitutes a disorder, and what represents a treatment, enablement and/or enhancement. Ethical issues may also arise from the (mis)use of biomarkers and endophenotypes in predicting and treating mental disorders, and what such definitions, predictions and interventions portend for concepts and views of criminality, professional competency and social functioning. Given these issues, we offer that a preparatory neuroethical framework is required to define and guide the ways in which RDoC- oriented research can – and arguably should - be utilized in clinical psychiatry, and perhaps more broadly, in the social sphere.

ABBREVIATIONS

RDoC: Research Domain Criteria; DSM: Diagnostic and Statistical Manual; NIMH: National Institute of Mental Health; ICD: International Classification of Diseases; BRAIN: Brain Research through Advancing Innovative Neurotechnologies initiative

INTRODUCTION

In 2008, the National Institute of Mental Health (NIMH) introduced a new strategic plan to close an evident gap between extant research-based and –derived information and knowledge of brain structure and function and the use of such information in clinical neuropsychiatric diagnoses and therapeutics. In so doing, the intent and hope was to establish a path toward both

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enhancing research and improving evidence-based mental health care [1].The Research Domain Criteria (RDoC) initiative is the practical execution of Objective 1.4 of this plan to "implement, for research purposes, a classification system based upon dimensions of observable behavior and neurobiological measures" (http:// www.nimh.nih.gov/about/strategic-planning-reports/index. html). Although still in early stages of development, the RDoC project has attracted widespread attention as it reflects something of a paradigm shift in approaching mental illness. While a detailed description of the RDoC initiative can be found elsewhere (see [2] for an overview), this essay provides a brief rationale for the development of the RDoC initiative, and highlights some conceptual, neuroethical, and social issues

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that arise from the development and clinical adoption of this framework as a diagnostic nosology.

Rationale of the RDoC

Perhaps the most powerful impetus for considering RDoC has been the increasing gap between neuroscience research and mental health practice [3]. One view of why neuroscientific research has not incurred greater bearing upon the clinical practice of psychiatry is that research studies are mostly based on inadequately conceptualized psychiatric diagnoses, and have been focused on explaining those diagnoses, rather than seeking to conceptually refine them [2]. The classification system used in the American Psychiatric Association's Diagnostic and Statistical Manual (DSM) was rationalized in that it could afford diagnostic reliability [4]. However, the DSM system does not enable or facilitate neurobiologic differentiation of psychiatric disorders [5]. In light of this, the DSM classification system tends to create artificialized categories of mental disorders, which in many ways obfuscates their complexity, and in so doing, may sustain mental disorders as being mythical - in the strictest, and most literal sense (i.e., - as "explanatory fictions") [6]. This has had the greatest influence on research. Mixed monothetic/ polythetic criteria-based categorical approaches for defining a psychiatric disorder incorporated considerable symptom heterogeneity, co-morbidity, and trait variance in study populations, which produced similar degrees of variability in results (even for the most sophisticated assessment techniques of neuroscience), thereby decreasing their reliability, if not validity in certain instances.

To counter such problems, a research framework was required that could be liberated from current diagnostic nosology of the DSM (and International Classification of Disease, ICD) system, and which would be more inclusive of the growing body of neuroscientific findings addressing structural and functional substrates of psychiatric conditions. While broad in scope and relatively deep in focus, much of this neuroscientific information is relatively inchoate [7]. Thus, organization of this research literature, and resulting utilization of research findings to guide clinically applicable diagnostics and therapeutics will be important for furthering particular trajectories of research inquiry and discovery. We posit that developing, specifying and prudently employing RDoC may meet such aims.

Undergirding these issues is the complexity of the brain, which is reflected not only in the arduousness of attempting to elucidate structural and functional correlates of cognitions, emotions and behaviors, but also by the diversity of human neuro-cognitive functions and expressions. Attempts at explaining this diversity have often engaged the biopsychosocial model [8]. Although views of the biopsychosocial model remain equivocal, a fundamental conceptualization of neuro-psychiatric function as obtaining and entailing interactive biological, cognitive and social dimensions is held to be sound [9,10]. While the DSM-5 has maintained clear distinctions between biological and psychological bases of mental illness, the RDoC initiative envisions the biopsychosocial model as an integrative framework, which does not establish rigid distinctions between physiologic, cognitive and environmental/ecological factors in and/or as origins of mental illness, but rather fosters and sustains a more interactive and reciprocal approach to these dimensions. In this way, RDoC-based classifications, unlike the DSM-5 which has remained "atheoretical", can become "theoretical" views of the etiology of mental illness. The RDoC attribute diversity of behavior, cognition (and emotion) to variability in/of human genomics, epigenetic modifications (and gene-environment interactions [11]), which lead to differential gene expression, neurogenesis, and phenotypic maturation of neural networks across the life span.

This diversity does not end at (the presence or absence of) a neural circuit; in fact it is further enriched by variable levels of function of individual neural circuits and complex interactions of different neural circuits throughout an individual's life. Consistent with such an understanding of the biopsychosocial model, the RDoC framework employs a dimensional approach to understanding and classifying psychopathology, utilizing seven levels (units) of analysis: genes, molecules, cells, circuits, physiology, behavior, and self-reports, to conceptually refine several psychological constructs and sub-constructs such as "acute threat", "frustrative non-reward" or "agency" (see https:// www.nimh.nih.gov/research-priorities/rdoc/constructs/ rdoc-matrix.html for an overview of the RDoC matrix). These psychological constructs will eventually become the fundamental units upon which psychopathology will be conceptualized and classified. Overall, the RDoC paradigm seeks to investigate and understand how each dimension contributes to a multitude of behavioral trajectories, without (necessarily) considering current psychiatric nosology (i.e. not labeling a behavioral trajectory as normal or abnormal). Each dimension can then serve as a possible point of diagnosis and treatment of psychiatric disorders which, themselves, will be re-defined by the RDoC framework [7,12]. In this light, RDoC may provide a means to develop greater precision within psychiatry, such that psychiatric diagnoses will rely upon and reflect clinical signs and symptoms as well as neuroscientific data, and psychiatric treatments will be personalized, and focused upon both biological and psychosocial factors.

Conceptual, Methodological and Neuroethical Challenges to the Use of RDoC

The potential for RDoC to substantively change, if not revolutionize psychiatric diagnosis and care may be significant, but it must be emphasized that the phenomena that RDoC are seeking to understand have complex theoretical, practical and social dimensions. As such, the viability and value of RDoC might warrant a higher level of scrutiny. We believe that this is important, as timely recognition of issues allows a constructive rather than merely a polemical orientation. At present, there is extensive discourse addressing conceptual and methodological challenges generated in and from the RDoC framework [11-20]. One of the clearest challenges to using RDoC is to prove the capability that is claimed. In other words, success of the RDoC framework is contingent upon the expanding capabilities of neuroscience to accurately describe and define neural mechanisms of psychiatric normality and abnormality.

Current neuroscientific techniques and technologies, and further progress toward using such approaches for structural and functional brain mapping, and for developing a variety

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of interventions are anticipated as a consequence of studies supported via the Brain Research through Advancing Innovative Neurotechnologies (BRAIN) initiative [21, 22]. However, the question of whether the tools of neuroscience will be able to objectivize psychiatry to the extent promised by the RDoC approach is a matter of ongoing debate and concern. For example, it remains uncertain if subjective experience can be quantified – or perhaps validated -through the use of assessment neurotechnologies. Although attempts toward this goal have shown some promise, neurotechnology is not, nor should not be regarded as superseding the importance and value of patients' first person experience.

This issue is both practical and philosophical; a subjectivist view of conscious experience incorporates some element of Cartesian dualism, implying that mental events cannot be quantified through the laws of physics. On the other hand, a materialist view of conscious experience does not necessarily account for the "qualia" of mental events, which have been, and continue to be focal to psychiatric nosology and practices. Kozak and Cuthbert [2] have attempted to find a middle ground between traditional phenomenology and materialism which they refer to as heterophenomenology. As consistent with the concept of heterophenomenology [23], the RDoC initiative seeks to include self-report as a unit of analysis, but accords self-report data no special precedence among different classes and types of measurement, and in fact, maintains theoretical neutrality among employed units of analysis.

In this light, the heterophenomenologic orientation may be particularly well suited for achieving the RDoC goal of elevating contributions of neuroscience to be constituent to an integrative approach to psychopathology. But this too is not without challenges, most notable of these, we believe, being the issue of dissonance (i.e.-modest covariation) among units of analysis, which can lead to decreased convergent validity of the constructs of the RDoC framework. [2]. We posit that this likely reflects an "explanatory gap" [24], and prompts the question of whether clinical applications and use of RDoC should be kept in abeyance until this explanatory gap is bridged in some way(s). If the RDoC framework is prematurely implemented in clinical realms, psychiatric practice may witness a misalignment of subjective self-reports and objective data. Will RDoC-based nosology maintain neutrality among units of analysis in the inference of diagnosis? Or, will it give preference to subjective symptoms?

We posit that in the presence of such dissonance and the "explanatory gap", the RDoC-based stance of maintaining theoretical neutrality among units of analysis may prove ethically challenging. Perhaps then, the solution to this problem actually does lie in reducing the extant explanatory gap between objective features of the nervous system and subjective experiences of cognition and emotions. However, it is crucial to ask if this gap can and will be bridged, and in the event, how long will this take, and what of clinical diagnosis and care in the interim? Answering these queries is critical in view of the current status of psychiatry and mental health, and the potential world-wide impact of the RDoC initiative. But such attempts at cutting through the problem of the explanatory gap may be double-edged: on the one side devoting attention to methods and metrics to de-limit dissonance and the explanatory gap will foster a more dedicated involvement in the validity and viability of RDoC; while on the other, such efforts may divert research foci away from the assessment and treatment of mental health problems, per se.

In our view, the RDoC framework represents an organized and effective approach to describing and defining psychiatric states, and we believe that at present, no viable alternative is more aptly suited for this purpose. However, axiomatic to our stance (if not the very notion of RDoC) are questions of if and how such criteria may be directed and utilized toward both "bench" as well as "bedside" aspects (and needs) of psychiatry. The neurosciences have certainly shown rapid and broad growth, but there is some debate as to whether research developments in the brain sciences have been influential to, or applied in clinical psychiatry [3], and there has been criticism of the NIMH's policy of shifting its funding away from DSM-based clinical research toward RDoC-oriented studies [25,26].

To wit, a more balanced approach, which considers both current mental health problems and RDoC objectives may be required. Thus, we concur with Patrick and Hajcak [14] that strategic steps should be taken to align RDoC research with clinical problems encountered in psychiatric practice. For this purpose, current mental health problems need to be defined and contextualized within the RDoC framework. However, it is important to ask how RDoC will discern abnormality from normality. Will distinctions be established at the extremes of cognitive and/or behavioral spectra, or will thresholds be drawn based upon psycho-socio-cultural norms and individual subjective experiences? To be sure, conceptualization of mental phenomena will require special attention to environmental and social contexts in which an individual's brain develops and functions. Social values will continue to play a role in defining a mental disorder [9]. Therefore, it is probable that the conceptual and ethical issues related to the definition of mental disorder, such as what constitutes treatment, enablement and/or enhancement, and a growing "medicalization of behavior", will persist in RDoCbased psychiatric nosology [27,28].

At present, it is unclear how RDoC constructs will map to psychiatric symptoms and disorders. Will RDoC constructs such as "agency" or "self knowledge" become the explanans of complex mental phenomena such as delusions, depersonalization, or personal identity? Although mechanistic reductionism (i.e. approaching complex phenomena through their components) may be a valid approach for attempting to understand mental function and disorders, RDoC must not lose sight of the complexities inherent to mental illness and the sufferings of patients, as commonly encountered in clinical practice. Thus, both "bottom up" (e.g. - identifying genotypic and phenotypic variables contributory to particular psychopathologies and/ or their treatment), and "top down" approaches (e.g. - studying the changes in functional organization of brain caused by psychotherapy) will be essential in this regard [29]. Moreover, given the plastic nature of the brain, the integration of psychosocial and environmental contexts with neurobiological functions in the RDoC framework remains challenging. Theoretically, "Big Data" approaches could offer some promise in integrating differing types and levels of information (i.e.- from the cellular to the

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social), but these too are not without issues or problems (the scope and extent of which are beyond the aim and focus of this essay [30]; see [31]for overview).

It is worth speculating whether the ability of RDoC-based psychiatric nosology could replace clinical utility of the DSM-5.The "operational revolution" brought on by the DSM-III increased the relative value of its constructs and categorizations to psychiatrists, psychotherapists and mental health counselors [17].Most of the constructs of RDoC have their origins in cognitive neuroscience, and their utility in and for clinical psychiatry remains debatable. Therefore, any attempt at clinical application of these constructs would require development of instruments to measure them in effective ways. In light of this, more widespread implementation of a neuroscientifically-based classification system might mandate increased focus on the neurosciences in medical education and psychiatry residency curricula [32]. But here too, it will be important not to lose sight of a biopsychosocial orientation that accurately nests neurobiological functions (and dysfunction) within the reality of an embodied, socioenvironmentally embedded individual who is the psychiatric patient.

Neuroethical, Legal and Social Implications of RDoC Based Psychiatric Nosology

Perhaps the most salient question is whether medicine and society are ready for a truly neuroscientifically-based psychiatry. In posing this question, let us engage a brief thought experiment: Imagine an era of precision psychiatry wherein a disorder can be predicted well before symptomatic onset. Even if researchers and clinicians are clear about the probabilistic nature of biomarkers, it would be easy for the public to overestimate their predictive ability. For example, it might become common practice to label children and adolescents "at risk" for certain disorders, or to even consider "at risk" to be synonymous with a pro-dromal phase of a particular disease. While such classifications may enable early - and preventive - intervention, they could also lead to stigmatization and distinctions in social regard and treatment even before the presentation of signs and symptoms. Such bias could evoke social discrimination, rejection, self-isolation, and loss of self-esteem of those persons who present accepted "indicators" of disorders, but are not yet considered to be patients [33]. Such characterizations could affect family dynamics, and parental attitudes towards, and care of "at risk" children [34].

Given the potential for these personal and social effects, we assert that it will be important to ascertain the extent to which neuroscience research can affect certain aspects of individual and public life [35,36]. Obviously there are calls for neuroscientific research to be directed toward identifying objective markers of socially harmful behaviors, such as violence and criminality, in order to employ neuropsychiatry as - and in - a more expansive construct and execution of public good (i.e.- as means to effect public safety)[37]. However postures of employing neuropsychiatry for "delivering humanity from evil" are likely to witness conflicts that arise in the juxtapositioning of an ethos of care, social justice and respect for individual autonomy [38]. Similarly, applications of neuroscientific research that focus upon psychopathologies relevant to criminal law are likely to sustain

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current, and invoke new debates regarding free will, capacity, and whether the use of neuro-psychiatric intervention constitutes rehabilitation or a masked form of retribution [39]. Ethical issues related use of neuroscientific approaches for cognitive performance optimization and/or emotional modification (i.e.-"cosmetic neuropsychiatry") will also arise [40,41].

The pace of neuroscientific research and the urgency of calls for its translation to improve neuropsychiatric diagnoses and treatment(s) mitigate a "wait and see" attitude, or use of a simple precautionary principle to guide the use of brain science in clinical psychiatry. Rather, we have argued that such issues call for a preparatory neuroethical stance that can be used to (a) realistically assess the potential of objective measurements of neurotechnology to be used in clinical realms; (b) chart trajectories of their use and misuse; (c) identify potential problems and issues arising from their use and misuse; and (d) develop guidelines and approaches to address these problems and issues before or early in their development [42]. Early public engagement and interdisciplinary interactions among neuroscience researchers, psychiatrists, social scientists, ethicists, legal scholars, and policymakers will be essential for both productive discourse and the formulation of reasoned outcomes.

Yet, even if consensus among these groups is reached about how neuroscientific information should be used in clinical psychiatry, it is important to recognize that commercial entities can utilize neuro-psychiatric data to define, depict and perhaps predict cognitions, emotions and behaviors for purposes that are aligned more with business ends than those of medicine [43]. Commercial entities can use algorithms to detect profiles of people with mental illnesses, to effect "profiling" and bias (if not frank discrimination) in employment and in the provision (and/ or denial) of health insurance. In the United States, the Genetic Information Non-Discrimination Act (GINA) protects against any such bias based on genetic information. We believe that similar legislation, such as the proposed Neuro Information Non-Discrimination Act (NINA) would be of value to protect individuals against bias educed by neuropsychiatric data [44]. Last, but certainly not least, a mental health agenda of this magnitude necessitates (if not obligates) increased funding initiatives, and the appropriation and allocation of resources as required to both initiate and sustain these multi-disciplinary efforts. Mental health reforms, such as the Mental Health Reform Act of 2016 are aimed at integrating mental health and primary care, and at increasing insurance coverage, without discrimination, as needed to implement equitable efforts in psychiatric diagnosis and treatment.

CONCLUSION

Psychiatry has been increasingly focused upon managing mental disorders in ways that reflect biological and psychosocial factors. Given prior shortcomings of psychiatric research and practice, such a precision approach is both welcomed, and viewed with some consternation. Concerns arise as to how psychiatric disorders will be characterized, diagnosed and treated in light of new findings from the brain sciences. RDoC have been posited as offering a viable pathway toward precision psychiatry. However, it is as yet unclear whether the adoption and use of RDoC represents a realistic, but challenging undertaking (i.e.,- a so-called medical "mission to the Moon"), a Herculean task that could be accomplished- although not in the immediate future (i.e.- a medical "mission to Mars"), or something Sisyphean at best, and impossible at worst (i.e.- a medical "mission to another universe").

We assert that both pragmatic enthusiasm and prudent criticism are required for strategically guiding this mission in the right direction(s). Tactical steps need to be taken in order to align research with needs of psychiatric practice. Neuroethical, legal and social issues must be identified and addressed early and often in this process. Finally, implementation of such a model of RDoC-based precision psychiatry will necessitate interdisciplinary and public engagement, and changes in both the culture of psychiatry, and in those policies that guide and govern research, clinical care, use of medical information and the public health. We believe that developing and using RDoC to establish new bases and categorizations of psychiatric disorders - and to guide more neurobiologically oriented, ontologically medical psychiatric diagnoses and care - is important and necessary to sustaining psychiatry as a technically and ethically sound practice to provide safe, effective and efficient public good.

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